IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Vijay Kumar HANDA et al.	Confirmation No.:
Application No.:	10/735,892	Group Art Unit:
Filing Date:	December 16, 2003	Examiner:
For:	A PROCESS FOR PREPARING FLORFENICOL	Attorney Docket No.: 7893-4000

SUBMISSION OF PRIORITY DOCUMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Applicant has claimed priority under 35 U.S.C. § 119 to Indian Application No. 806/MAS/2003, filed on October 6, 2003. In support of this claim, a certified copy of this application is submitted herewith.

No fee or certification is believed to be due for this submission. Should any fee be required, however, please charge such fee to Winston & Strawn LLP Deposit Account No. 50-1814.

Respectfully submitted,

1/28/04
Date

Rodney J. Fuller (Reg. No. 46,714)
For: Allan A. Fanucci (Reg. No. 30,256)

WINSTON & STRAWN LLP
Customer No. 28765

202-371-5904

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification & Abstract of the extract of Patent Application No.806MAS/2003, dated 06/10/2003 by M/s. Aurobindo Pharma Limited, an Indian company having its registered office at Plot No.2, Maitrivihar Complex , Ameerpet Hyderabad –500 038 Andhra Pradesh, India.

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the 8th day of January 2004
18th day of pausa, 1925(Saka)

M. S. Venkataraman

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet,Chennai – 600 018

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT OFFICE
[See section 5(2), 7/54 and 135]

1. We

AUROBINDO PHARMA LIMITED
PLOT NO. 2, MAITRIVIHAR COMPLEX (Regd. Office)
AMEERPET
HYDERABAD – 500 038
ANDHRA PRADESH
INDIA
(An Indian Organisation)

2. Hereby declare: -

(a) That we are in possession of an invention titled: -

(b) **"A PROCESS TO PREPARE FLORFENICOL "**

(c) That the Complete Specification relating to this invention is filed with this application.

(d) That there is no lawful ground of objection to grant of a Patent to us.

3. Further declare that the inventor(s) for the said invention is: -

(a) **VIJAY KUMAR HANDA**

(b) **ARUN KUMAR GUPTA**

(c) **MEENAKSHISUNDERAM SIVAKUMARAN**

C/o. AUROBINDO PHARMA LIMITED
PLOT NO. 2, MAITRIVIHAR COMPLEX (Regd. Office)
AMEERPET
HYDERABAD – 500 038.
ANDHRA PRADESH
INDIA

(a) to (c) : **CITIZENS OF INDIA**

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows:-

(a) NIL

(b) NONE

5. We state that the said invention is an improvement in or modification of the particulars of which are as follows and of which we are the Applicant/Patentee:

(a) NIL

(b) NONE

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application be deemed to have been filed on .... under section 16 of the Act:

NONE

7. That we are the assignee or legal representative of the true and first Inventors.

8. That our addresses for service in India is as follows:

AUROBINDO PHARMA LIMITED
Plot No. 2, Maitrivihar Complex,
Ameerpet,
Hyderabad - 500 038
Andhra Pradesh
India
Phone No.: 91-40-23741083
Fax No. : 91-40-23741080, 23740591

9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:-

We the true and first inventors for the invention or the applicant(s) in the convention country declare that the applicant(s) herein are our assignee or legal representative:

(a) VIJAY KUMAR HANDA Vijay Kumar Handa

(b) ARUN KUMAR GUPTA

(c) MEENAKSHISUNDERAM SIVAKUMARAN

11. Following are the attachment with the application: -

(a) Complete Specification (3 copies).

(b) Drawings (NIL)

(c) Priority document(s)

(i) Fee Rs. 6000/- in Bank Draft bearing No 020414 dated 26/8/03 on State Bank of Hyderabad.

We request that a Patent may be granted to us for the said invention.

Dated this 29th day of September 2003.

.....
(Dr. M. SIVARAMAN)
DIRECTOR

TO
THE CONTROLLER OF PATENTS,
THE PATENT OFFICE,
CHENNAI

THE PATENT ACT, 1970

COMPLETE

SPECIFICATION

(SECTION 10)

TITLE

"A PROCESS TO PREPARE FLORFENICOL"

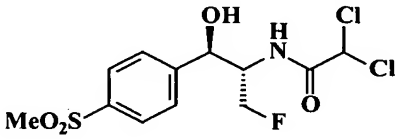
APPLICANT

AUROBINDO PHARMA LIMITED
HAVING REGISTERED OFFICE AT
PLOT NO. 2, MAITRI VIHAR COMPLEX,
AMEERPET, HYDERABAD – 500 038,
ANDHRA PRADESH, INDIA,
AN INDIAN ORGANIZATION

The following specification particularly describes and ascertains the nature of this invention and the manner in which the same is to be performed.

DESCRIPTION

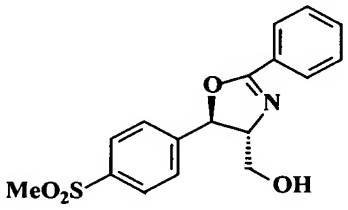
Florfenicol of Formula I, the fluoro derivative of thiamphenicol, is a broad spectrum antibiotic compound possessing activity against many Gram negative, Gram positive, and thiamphenicol-resistant microorganisms. Florfenicol, chemically known as (1*R*,2*S*)-2-dichloroacetamido-3-fluoro-1-[4-(methylsulfonyl)phenyl]-1-propanol, is of interest as a veterinary product.



Formula I

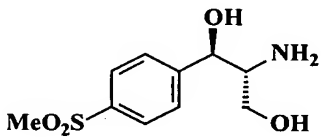
US Patent 4,235,892 describes a process to convert thiamphenicol into Florfenicol. The major drawback of this process was a poor fluorination step. The fluorination of *N*-protected compound, (1*R*,2*R*)-1-[4-(methylsulfonyl)phenyl]-2-phthalimido-1,3-propanediol, was accomplished with diethylamine sulfurtrifluoride (DAST), which was non-selective and led to a mixture of fluorinated products. The desired compound may thus be obtained at a sufficient purity by using complex column chromatography process. Also, it is hazardous and expensive to use DAST on a large scale.

An alternate approach to prepare Florfenicol has been described in US Patent 4,876,352 starting from (4*R*,5*R*)-4-hydroxymethyl-5-[4-(methylsulfonyl)phenyl]-2-phenyl-2-oxazoline of Formula III. This oxazoline has been prepared by simultaneously protecting



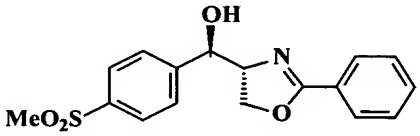
Formula III

the secondary hydroxyl group and the primary amino group present in (1*R*,2*R*)-2-amino-1-[(4-methylsulfonyl)phenyl]-1,3-propanediol of Formula IV as described in US Patent 5,227,494.



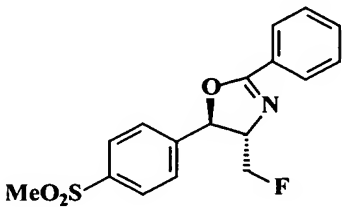
Formula IV

This preparation requires use of toxic benzonitrile and harsh reaction conditions like 18 hours heating at 115°C. Alternatively, the desired oxazoline has been prepared in the US Patent 4,743,700 using ethyl benzimidate hydrochloride. However, the yield obtained is low, the remainder being isomeric oxazoline of Formula V



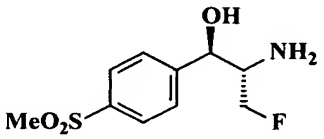
Formula V

Thereafter, this oxazoline has been conveniently converted to the corresponding fluoro oxazoline of Formula VI by reacting with Ishikawa reagent,



Formula VI

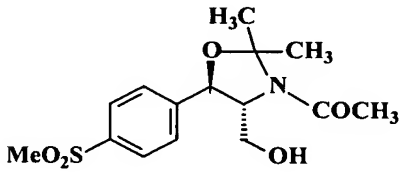
(1,1,2,3,3,3-hexafluoropropyl)diethylamine. After performance of fluorination step, the oxazoline is hydrolyzed to obtain amine of Formula VII. This removal of oxazoline



Formula VII

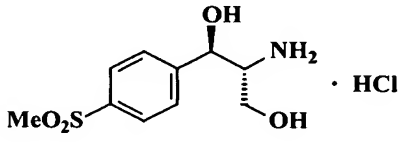
protecting group necessitates heating at 100°C for 18 hours with 12N hydrochloric acid that results in significant amount of by-product, 1,3-propanediol of Formula IV.

In view of the prior art described above, the present invention provides a new process for preparing highly pure Florfenicol starting from (1*R*,2*R*)-2-amino-1-[(4-methylsulfonyl) phenyl]-1,3-propanediol of Formula IV. In this process, the hydrogen atom of the secondary hydroxyl group and the one hydrogen atom of the primary amino group have been contemporaneously protected by acetonide formation and the second hydrogen atom of the primary amine has been derivatized with an acetyl group. This results in preparation of oxazolidine derivative, namely (4*R*,5*R*)-3-acetyl-2,2-dimethyl-4-hydroxymethyl-5-[4-(methylsulfonyl)phenyl]-1,3-oxazolidine of Formula II.



Formula II

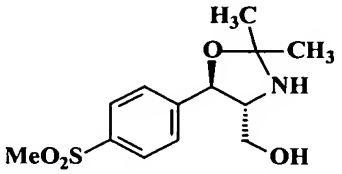
The present invention is directed towards a new process for preparing Florfenicol antibiotic. According to the present invention, a process is described to prepare a novel oxazolidine compound of Formula II that starts from (1*R*,2*R*)-2-amino-1-[(4-methylsulfonyl)phenyl]-1,3-propanediol hydrochloride of Formula VIII. The starting material of Formula VIII may be



Formula VIII

obtained from the commercially available thiamphenicol as described in the US Patent 4,235,892.

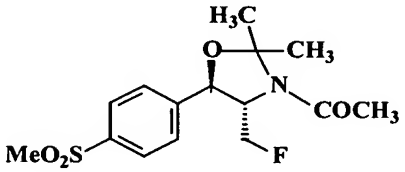
According to the instant invention, amino diol compound of Formula VIII is treated with an agent which can afford oxazolidine compound of Formula IX. It is preferred to use



Formula IX

acetone, 2-methoxypropene or 2,2-dimethoxypropane in presence of an organic base and a solvent wherein the said solvent is acetone, toluene, xylenes, hexanes or a mixture thereof. Preferably the base is an alkylamine and more specifically it is triethylamine. The most preferred technique to prepare oxazolidine compound of Formula IX is to heat aminodiol compound of Formula VIII with eight to ten times by volume of acetone which can react to produce oxazolidine, as cited above, and which may also act as solvent. The reaction is carried out at 50°C to 60°C in presence of 1.2 to 2.0 mole of triethylamine. This preparation has the advantage of being regio-selective, involves relatively mild reaction conditions and no racemization of the chiral starting material occurs. Subsequent to this reaction, *N*-acetylation in methylene chloride is performed with acetyl chloride and triethylamine base to obtain oxazolidine compound of Formula II in good yield.

Thereafter, the hydroxy compound of Formula II is converted to the corresponding fluoro derivative, (4*S*,5*R*)-3-acetyl-2,2-dimethyl-4-fluoromethyl-5-[4-(methylsulfonyl) phenyl]-1,3-oxazolidine, of Formula X , wherein the carbinol compound is reacted



Formula X

with (1,1,2,3,3,3-hexafluoropropyl)diethylamine fluorinating agent in an inert organic solvent under pressure conditions at elevated temperatures. The reaction is conducted in a closed system at 80°C to 110°C under pressure ranging from 60 psi to 100 psi. The suitable organic solvents are chlorinated hydrocarbons such as methylene chloride, chloroform, chlorobenzene and the like. The most preferred solvent is methylene chloride. The amount of fluorinating agent is preferably in excess over that required by stoichiometry. The molar ratio of (1,1,2,3,3,3-hexafluoropropyl)diethylamine to the hydroxy compound is 1:1 to 3:1 and preferably 2:1.

It may be noted here that absolute configuration of the two compounds of Formula II and Formula X is analogous while the apparent difference in the configuration of the atom at position 4 is due exclusively to rules of nomenclature.

After performance of fluorination step, the protective groups are removed from the compound of Formula X to obtain amine of Formula VII. The preferred method consists in removing the protecting groups with acids, preferably inorganic acids, in aqueous medium.

Fluoro oxazolidine of Formula X is advantageously hydrolyzed by heating with 6N aqueous hydrochloric acid at 90-100°C for 30 min.

Finally, the compound of Formula VII is acylated with dichloroacetic acid or with a reactive derivative thereof to prepare Florfenicol by the methods reported in art.

Preparation of novel oxazolidine compound of Formula II and its conversion to fluoro amine of Formula VII are the inventive steps of this Florfenicol synthesis. The major advantage realized in the present synthesis as compared to the prior art is the rapid hydrolysis of oxazolidine resulting in greater efficiency and higher product purity.

The new Florfenicol synthesis is illustrated by the following examples.

Example 1

PREPARATION OF (1R,2S)-2-DICHLOROACETAMIDO-3-FLUORO-1-[4-(METHYLSULFONYL)PHENYL]-1-PROPANOL *(FLORFENICOL)*

STEP-I:

PREPARATION OF (4R,5R)-3-ACETYL-2,2-DIMETHYL-4-HYDROXYMETHYL-5-[4-(METHYLSULFONYL)PHENYL]-1,3-OXAZOLIDINE *(N-ACETYL OXAZOLIDINE)*

A suspension of (1*R*,2*R*)-2-amino-1-[4-(methylsulfonyl)phenyl]-1,3-propanediol hydrochloride (50 g, 0.178 mole), triethylamine (35.88 g, 0.355 mole) and acetone (400 ml) were heated at 50°C to 60°C for 12 hours. The reaction mass was cooled to room temperature, filtered and the filtrate was evaporated under reduced pressure at 40°C to 45°C. The mass was dissolved in methylene chloride (450 ml) and to this solution triethylamine (26.91 g, 0.266 mole) and acetyl chloride (15.34 g, 0.195 mole) were added at 10°C to 15°C in an inert atmosphere. After completion of the reaction, the reaction mass was washed with 10% w/v aqueous ammonium chloride solution (100 ml) and the organic layer was evaporated to dryness. The residue was dissolved in methanol (150 ml) and stirred with potassium carbonate (9.8 g, 0.071 mole) for 30-35 minutes at 20°C to 25°C. The solvent was evaporated and the reaction mass was dissolved in methylene chloride (125 ml) and washed with water (25 ml). The organic layer was concentrated under reduced pressure to obtain viscous oil, which was crystallized from ethyl acetate (100 ml) to obtain the title compound (42.5 g, HPLC purity: 96.0%).

MELTING RANGE: 108°-115°C;
SPECIFIC OPTICAL ROTATION: $[\alpha]^{25}_{D}$: + 27.5° (C=0.5, Methanol)
^{1}H NMR (300 MHz) in *DMSO-d_6*: *δ(ppm)*; 1.52 (*s*, 3H, CH_3), 1.54 (*s*, 3H, CH_3), 2.06 (*s*, 3H, CH_3), 3.23 (*s*, 3H, CH_3), 3.66 (*brm*, 2H, CH_2), 4.15 (*brs*, 1H, H-4), 5.23 (*d*, J=3.3 Hz, 1H, H-5), 5.33 (*t*, J=5.4 Hz, 1H, OH), 7.73 (*d*, J=8.4 Hz, 2H, ArH); 7.95 (*d*, J=8.4 Hz, 2H, ArH).
MASS: m/z; 328 [$(MH)^+$]

STEP-II:

***PREPARATION OF (4S,5R)-3-ACETYL-2,2-DIMETHYL-4-FLUOROMETHYL-5-[4-(METHYLSULFONYL)PHENYL]-1,3-OXAZOLIDINE** (FLUORO OXAZOLIDINE)*

To a suspension of (4*R*,5*R*)-3-acetyl-2,2-dimethyl-4-hydroxymethyl-5-[(4-methylsulfonyl) phenyl]-1,3-oxazolidine (25 g, 0.076 moles) in methylene chloride (250 ml) under nitrogen atmosphere, was added (1,1,2,3,3,3-hexafluoropropyl)diethylamine (Ishikawa reagent, 34 g, 0.152 moles) in a closed reactor. The reactor was heated at 90°C to 100°C at 90 psi to 100 psi for 1 hour. The reaction mass was cooled to 0°C, washed with saturated sodium chloride solution (50 ml) and used as such in the next step.

STEP-III:

***PREPARATION OF (1R,2S)-1-[4-(METHYLSULFONYL)PHENYL]-2-AMINO-3-FLUORO-1-PROPANOL** (FLUORO AMINE)*

The organic solution (~275 ml, *as obtained above*) was added to 6N aqueous hydrochloric acid (250 ml) at 90°C to 100°C over a period of 30 min. and methylene chloride was distilled simultaneously from the reaction mass. After stirring at 90-100°C for another 30 min, the solution was cooled to room temperature and washed with dichloroethane (3x50 ml). The pH of the aqueous layer was adjusted to 12.0 at 5°C to 10°C with 50% w/v sodium hydroxide solution and extracted with methylene chloride (300 ml). The methylene chloride layer was concentrated to obtain the title compound as a residual solid (15 g, HPLC purity: 90.0%). Analytical sample was prepared by crystallization from isopropyl alcohol.

MELTING RANGE: 99°-103°C
SPECIFIC OPTICAL ROTATION: $[\alpha]^{26}_{D}$ -35.2° (C=0.5, Methanol)
^{1}H NMR (300 MHz) in *DMSO-d_6*: *δ(ppm)*; 1.56 (*brs*, 2H, NH_2), 2.97-3.05 (*m*, 1H, H-2), 3.2 (*s*, 3H, CH_3), 4.10-4.49 (*m*, 2H, CH_2, H-3), 4.71 (*d*, J=3.3 Hz, 1H, H-1), 5.7 (*brs*, 1H, OH), 7.62 (*d*, J=8.1 Hz, 2H, ArH), 7.95 (*d*, J=8.1 Hz, 2H, ArH).
MASS: m/z; 248 [$(MH)^+$]

STEP-IV:

***PREPARATION OF (1R,2S)-2-DICHLOROACETAMIDO-3-FLUORO-1-[4-(METHYLSULFONYL) PHENYL]-1-PROPANOL** (FLORFENICOL)*

To a solution of (1*R*,2*S*)-1-[4-(methylsulfonyl)phenyl]-2-amino-3-fluoro-1-propanol (5 g, 0.02 moles) in methanol (50 ml) was added methyl dichloroacetate (14.5 g; 0.10 g) and triethylamine (2.05 g, 0.02 mole) and stirred at room temperature for 18 hours. After completion of reaction, methanol was distilled off from the reaction mass, toluene (25 ml) and water (5 ml) were added. The product thus precipitated was filtered, washed with methylene chloride (20 ml) and crystallized from 2-propanol / water (5:1) to give 5 g of title compound having purity 99.20% by HPLC.

MELTING RANGE: 153°-154°C
SPECIFC OPTICAL ROTATION: $[\alpha]^{20}_{D}$ -18.2° (C=0.5, in *N,N*-dimethylformamide)
^{1}H NMR (300 MHz) in *DMSO-d_6*: *δ(ppm)*; 3.17 (*s*, 3H, CH_3), 4.29-4.76 [*m*, 3H, H-2 and H-3(CH_2)], 4.99 (*brs*, 1H, H-1), 6.16 (*d*, J=2.7 Hz, OH), 6.46 (*s*, 1H, $CHCl_2$), 7.62 (*d*, J=6.9 Hz, 2H, ArH), 7.86 (*d*, J=6.9 Hz, 2H, ArH), 8.62 (*d*, J=8.4 Hz, NH).
MASS: m/z; 358 [$(MH)^+$], 360 [$(MH+2)^+$], 362 [$(MH+4)^+$]

Example 2

PREPARATION OF (4R,5R)-3-ACETYL-2,2-DIMETHYL-4-HYDROXYMETHYL-5-[4-(METHYLSULFONYL)PHENYL]-1,3-OXAZOLIDINE *(N-ACETYL OXAZOLIDINE)*

A suspension of (1*R*,2*R*)-2-amino-1-[4-(methylsulfonyl)phenyl]-1,3-propanediol hydrochloride (50 g, 0.178 mole), triethylamine (35.88 g, 0.355 mole), acetone (250 ml) and toluene (250 ml) were heated at 70-80°C for 18 hours. The reaction mass was cooled to room temperature, filtered and the filtrate was evaporated under reduced pressure at 40°C to 45°C. The mass was dissolved in methylene chloride (450 ml) and to this solution triethylamine (26.91 g, 0.266 mole) and acetyl chloride (15.34 g, 0.195 mole) were added at 10°C to 15°C in an inert atmosphere. After completion of the reaction, the reaction mass was washed with 10% w/v aqueous ammonium chloride solution (100 ml) and the organic layer was evaporated to dryness. The residue was dissolved in methanol (150 ml) and stirred with potassium carbonate (9.8 g, 0.071 mole) for 30-35 minutes at 20°C to 25°C. The solvent was evaporated and the reaction mass was dissolved in methylene chloride (125 ml) and washed with water (25 ml). The organic layer was concentrated under reduced pressure to obtain viscous oil, which was crystallized from ethyl acetate (100 ml) to obtain the title compound (40 g, HPLC purity: 97.3%).

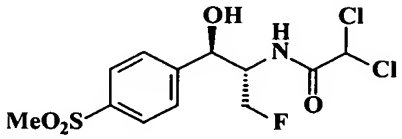
Example 3

PREPARATION OF (1R,2S)-2-DICHLOROACETAMIDO-3-FLUORO-1-[4-(METHYLSULFONYL)PHENYL]-1-PROPANOL *(FLORFENICOL)*

To a solution of (1*R*,2*S*)-1-[4-(methylsulfonyl)phenyl]-2-amino-3-fluoro-1-propanol (5 g, 0.02 moles) in methanol (50 ml) was added methyl dichloroacetate (14.5 g; 0.10 g) and heated to reflux at 60°C to 65°C for 18 hours. After completion of reaction, methanol was distilled off from reaction mass, toluene (25 ml) and water (5 ml) were added. The product thus precipitated was filtered, washed with methylene chloride (20 ml) and crystallized from 2-propanol / water (5:1) to give 5 g of Florfenicol with 99% HPLC purity.

WE CLAIM

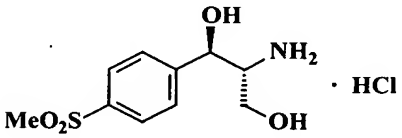
1) A process for the manufacture of Florfenicol of Formula I



Formula I

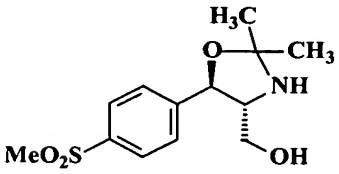
which comprises the following steps:

(a) converting the compound of Formula VIII



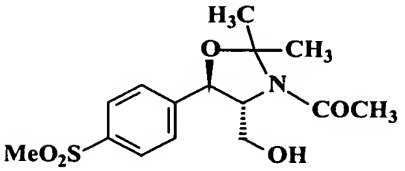
Formula VIII

into oxazolidine derivative of Formula IX



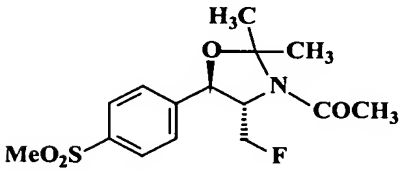
Formula IX

(b) acylating compound of Formula IX to *N*-acylated oxazolidine derivative of Formula II



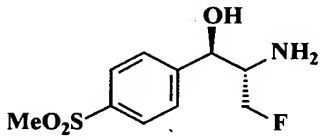
Formula II

(c) fluorinating the compound of Formula II to the corresponding fluoro oxazolidine of Formula X



Formula X

(d) hydrolysis of fluoro oxazolidine of Formula X to amine of Formula VII



Formula VII

and

(e) *N*-acylation of amine of Formula VII to Florfenicol.

2) A process according to Claim 1, wherein in the compound of Formula IX is obtained by reacting the compound of Formula VIII with acetone at 50°C to 60°C in presence of triethylamine.

3) A process according to Claim 1, wherein the compound of Formula IX is acylated with acetyl chloride.

4) A process according to Claim 1, wherein the fluorination of compound of Formula II is carried out using (1,1,2,3,3,3-hexafluoropropyl)diethylamine.

5) A process according to Claim 4, wherein the fluorination is carried out in methylene chloride at 80°C to 110°C at a pressure of 60 psi to 100 psi.

6) A process according to Claim 1, wherein the fluoro oxazolidine of Formula X is hydrolyzed with aqueous hydrochloric acid.

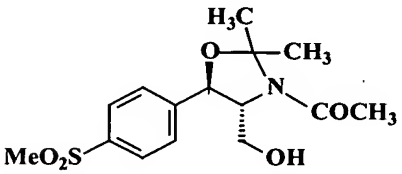
7) A process according to Claim 6, wherein the hydrolysis is carried out at 90°C to 100°C.

8) A process according to Claim 1, wherein the *N*-acylation of compound of Formula VII is carried out with dichloroacetic acid or with a reactive derivative thereof.

9) A process according to Claim 8, wherein the *N*-acylation is optionally carried out in presence of triethylamine.

10) A process of preparing Florfenicol substantially as described herein.

11) A compound of Formula II



Formula II

useful in the preparation of Florfenicol.

Dated this the 6th day of October 2003

AUROBINDO PHARMA LIMITED

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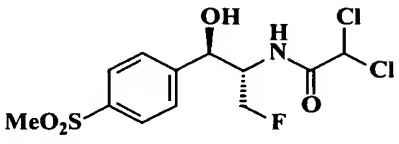
Ms. NANDA BHASKARA
LEGAL OFFICER
FOR THE APPLICANTS

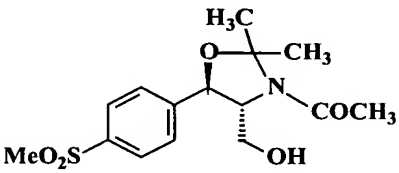
ABSTRACT

A new synthesis is disclosed for the preparation of a broad spectrum antibiotic, Florfenicol of Formula I



Formula I

that makes use of a novel *N*-acylated oxazolidine derivative, namely (4*R*,5*R*)-3-acetyl-2,2-dimethyl-4-hydroxymethyl-5-[4-(methylsulfonyl)phenyl]-1,3-oxazolidine, represented by Formula II



Formula II

A process to prepare oxazolidine derivative of Formula II is also described.